PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 28113/39467A	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/EP2004/008819	International filing date *(day/month/year)* 06 August 2004 (06.08.2004)	Priority date *(day/month/year)* 08 August 2003 (08.08.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant LICENTIA, LTD.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 13 February 2006 (13.02.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 740 14 35	Authorized officer Ellen Moyse Telephone No. +41 22 338 89 75

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

5

REC'D 28 DEC 2004
WIPO PCT

PCT

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

17/2

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/008819	06.08.2004	08.08.2003

International Patent Classification (IPC) or both national classification and IPC
C12Q1/68

Applicant
LICENTIA, LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Barz, W Telephone No. +49 89 2399-7320

Form (PCT/ISA/237) (Cover Sheet) (January 2004)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☐ The following document has not been furnished:

   ☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☒ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 3-15, 17-46, 74-78 (IA)

because:

☒ the said international application, or the said claims Nos. 3-15, 17-46, 74-78 (IA) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-45,52-53,57-78
	No:	Claims	46-51,54-56
Inventive step (IS)	Yes:	Claims	1-45,67-78
	No:	Claims	46-66
Industrial applicability (IA)	Yes:	Claims	1-2,16,47-73
	No:	Claims	

2. Citations and explanations

see separate sheet

CORRECTED VERSION

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/EP2004/008819

ITEM III:

Due to the expressions "obtaining the biological sample comprising [...]" and/or "administering to a subject [...]", **claims 3-15, 17-46, and 74-78** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT). See, however, item V-3. below.

ITEM V:

Reference is made to the following documents:
D1: WO 03/27285 (Bionomics Ltd.), 3. April 2003;
D2: US2003/087807 (Greenspan R.J.); 8. May 2003;
D3: EMBO Journal, vol. 21, 2002, pages 4593-4599; (Petrova T.V. et al.);
D4: Developmental Dynamics, vol. 225, 2002, pages 351-357; (Hong Y.K. et al.);
D5: EMBO Journal, vol. 21, 2002, pages 1505-1513; (Wigle J.T. et al.).

1. NOVELTY

Claims 46-51 and 54-56 which are not restricted to the correlation between Prox-1 expression and colorectal cancer, do not meet the requirements of Article 33(2) PCT for the following reasons:

1.1 A method of inhibiting Prox-1 function comprising all features of present **claim 46** are known from document D1 (page 14, lines 1-14; page 15, lines 1-11; BNO368 in Table 2 (page 53); claims 2, 35, and 55). Therefore, said claim is not novel in the sense or Article 33(2) PCT.

1.2 Similarly, the second medical use as in present **claim 47** is also known from D1 (page 14, lines 15-22, claims 2 and 77).

1.3 Methods of screening Prox-1 modulators (i.e. compounds binding to Prox-1)

CORRECTED VERSION

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/EP2004/008819

comprising all features of **claims 48-51 and 54-55** are also known from D1 (claims 34-36, 41, and 44) as well as from document D2 (claims 15, 17, and 51).

1.4 **Claim 56** relates to a siRNA molecule comprising a sense region and an antisense region complementary to each other, wherein the antisense region is also complementary to a sequence comprising SEQ ID NO:2. Since, however, such siRNA is known from D1 (see page 15, lines 1-6; SEQ ID NO:102; claim 2), novelty of said claim cannot be acknowledged.

1.5 **Claims 1-45, 52-53, and 67-78** meet the requirements of Article 33(2) PCT, because none of the available prior art documents discloses screening methods, growth inhibition methods, or second medical uses comprising the same combinations of features (including the correlation between Prox-1 expression and colorectal cancer) as in said claims.

2. INVENTIVE STEP

Claims 52-53 and 57-66 do not appear to meet the requirements of Article 33(3) PCT for the following reasons:

2.1 Document D3, which is regarded as being the closest prior art for present **claim 52**, discloses (see title) that Prox-1 is a transcription factor, i.e. that it is able to bind to DNA. Compared to said prior art document, the subject-matter of said claim differs only by the screening for modulators which decrease or increase said binding of Prox-1 to DNA. Given, however, the known DNA-binding competence of the transcription factor Prox-1, it would be obvious for the skilled person to screen to modulators decreasing or increasing said binding. Therefore, the involvement of an inventive step (Article 33(3) PCT) cannot be acknowledged for claim 52.

2.2 An analogous objection applies to present **claim 53**, because the role of Prox-1 in differentiation is well-known from the prior art (e.g. from documents D3-D5 disclosing the role of Prox-1 in lymphatic endothelial cell differentiation).

2.3 The dependent **claims 57-66** do not contain any features which, in combination with

CORRECTED VERSION

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/EP2004/008819

the features of claim 56 to which they refer, meet the requirements of the PCT with respect to inventive step (Article 33(3) PCT), because the additional features of said claim represent standard modifications which the skilled person would select, in accordance with circumstances and without the exercise of inventive skill.

2.4 In contrast, **claims 1-45 and 67-78** appear to fulfill the requirements of Article 33(3) PCT, because the prior art does not seem to disclose the correlation between elevated Prox-1 expression and colorectal cancer. Therefore, the skilled person would have no incentive (i) to screen colon tissue for colorectal cancer by measuring Prox-1 overexpression (**claims 1-15**); or (ii) to inhibit the growth of colorectal cancer cells by suppressing Prox-1 expression/activity (**claims 17-31, 33-34, 36-38, 40-41, 43-45, 74-76, and 78**). Analogous arguments apply to the use of molecules suppressing Prox-1 expression/activity in the manufacture of medicaments for the treatment of colorectal cancer (**claims 16, 18-30, 32, 35-37, 39-40, 42-45, 67-75, and 77-78**).

3. INDUSTRIAL APPLICABILITY

For the assessment of the present **claims 3-15, 17-46, and 74-78** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment. Furthermore, the EPO does not recognize as industrially applicable the subject-matter of claims to the treatment of the human or animal body by surgery (see item III above).

4. FURTHER COMMENTS

4.1 **Claims 1-3** do not fulfill the requirements of Articles 5 and 6 PCT, because a

CORRECTED VERSION

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/EP2004/008819

correlation between Prox-1 expression and "a pathological condition/phenotype" is neither disclosed in the present application nor supported by the present description. Therefore, said claims should be restricted to the screening of colon tissue for colorectal cancer (as in present claim 4).

4.2 The term "-catenin/TCF" used in **claims 12-13 and 34-37** is not clear (Article 6 PCT) and appears to lack an Greek letter (ß as discloses in example 5, for example?) in front of it.

4.3 **Claim 48** is not clear (Article 6 PCT), because "contacting a test molecule with Prox-1 [...] under conditions which permit the interaction [...] and measuring interaction between [...]" (underlining added) will find interaction between Prox-1 and any test molecule, and thus not be able screen for Prox-1 modulators. Consequently, said claim should be reworded appropriately.

4.4 The term "fragment" used in **claims 56 and 70** does not fulfill the requirements of Article 6 PCT, because the subject-matter for which protection is sought is not clear as long as the minimal length of such a fragment is not indicated. As a single nucleotide or amino acid could be regarded as a "fragment" of a polynucleotide, the skilled person would regard every prior art polynucleotide as falling under the wording of said term.

4.5 **Claims 71-73** do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved ("comprises a promoter or other control region, an exon, an intron, or an exon-intron boundary", "an exon-intron splice junction"), which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

CONCLUDING REMARKS:

a) New claims to be filed should take account of all of the above comments.

CORRECTED VERSION

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/EP2004/008819

b) Amendments should be filed by way of replacement pages.

c) In the reply, those parts of the application as originally filed which form a basis for the amendment should be indicated (Article 34(2)(b) PCT; Rule 66.8(a) PCT). In the absence of such indications, the amendments may be disregarded when issuing the International Preliminary Examination Report.